Peripheral Arterial Disease, Acute Coronary Syndromes, and Early Invasive Management: The TACTICS TIMI 18 Trial

JAMES L. JANUZZI, JR., M.D., JACQUELINE BUROS, B.A.,* CHRISTOPHER P. CANNON, M.D.,* ON BEHALF OF THE TACTICS TIMI 18 INVESTIGATORS

Cardiology Division, Massachusetts General Hospital, and *TIMI Group, Brigham and Women's Hospital, Boston, Massachusetts, USA

Summary

Background: Patients with peripheral arterial disease (PAD) represent a high-risk patient subset in the setting of non-ST-segment elevation acute coronary syndromes (NSTEMI/ACS). The efficacy and safety of early invasive management for such patients remains unclear.

Hypothesis: Early invasive management would be well tolerated and effective among patients with NSTEMI/ACS and PAD.

Methods: Patients from the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction (TACTICS-TIMI) 18 trial were stratified by the presence or absence of PAD and assessed with respect to baseline clinical factors. The outcomes of patients with PAD and NSTEMI/ACS were examined with respect to treatment assignment to either early invasive therapy or conservative treatment of NSTEMI/ACS. Finally, the bleeding and stroke rates of patients with PAD managed invasively were compared with patients with PAD managed conservatively.

Results: Of 2,219 patients with NSTEMI/ACS overall, 166 (7.5%) had concomitant PAD. Compared with those patients without PAD, those with PAD were older (75 vs. 62 years, $p < 0.001$) and were more likely to have high-risk clinical features, including prior histories of bypass surgery (39 vs. 20%,

$p < 0.001$) or diabetes mellitus (38 vs. 27%, $p = 0.002$), and more ST-segment depression on their 12-lead electrocardiogram (43 vs. 29%, $p < 0.001$). Among such patients, early invasive management was associated with significant reductions in the risk of myocardial infarction (MI) at 30 days (11.4 vs. 2.3%, $p = 0.03$). At 180 days, compared with early conservative management, early invasive treatment for patients with PAD and NSTEMI/ACS was associated with similar reductions in MI (12.7 vs. 3.5%, $p = 0.04$), and was also accompanied by significant reductions in risk of death (10.1 vs. 2.3%, $p = 0.05$). No excess in bleeding or stroke rates was noted among patients with PAD managed invasively.

Conclusions: Among patients with NSTEMI/ACS and a history of PAD, early invasive management is well tolerated and accompanied by significant reductions in morbidity and mortality when compared with a more conservative, ischemia-driven approach.

Key words: acute coronary syndromes, glycoprotein IIb/IIIa receptor antagonists, peripheral arterial disease, outcomes

Introduction

The presence of peripheral arterial disease (PAD) is a marker of high risk for adverse outcomes among patients with non-ST-segment elevation acute coronary syndromes (NSTEMI/ACS).¹ This is believed to reflect the higher prevalence of complex cardiac risk factors among patients with PAD.² Furthermore, the presence of diffuse atherosclerosis increases the risk for invasive management strategies for revascularization, such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).^{3–6} Therefore, the identification of optimal therapeutic strategies for this population is particularly challenging.

Limited prior data suggest that therapy with the platelet glycoprotein (GP) IIb/IIIa receptor inhibitor tirofiban is effective and well tolerated by patients with PAD undergoing peripheral arterial angiography and revascularization.⁷ However, it remains unclear whether patients with NSTEMI/ACS and PAD treated with GP IIb/IIIa receptor antagonists and inva-

Address for reprints:

James L. Januzzi, Jr., M.D.
Cardiology Division
Massachusetts General Hospital
Jawkey 5984
55 Fruit Street
Boston, MA 02114, USA
e-mail: jjanuzzi@partners.org

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sive management strategies would have favorable outcomes. Therefore, we undertook the present analysis from the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) Thrombolysis in Myocardial Infarction (TIMI) 18 trial,⁸ to assess the benefits and tolerability of GP IIb/IIIa receptor antagonism together with early invasive management among patients with PAD and NSTEMI ACS.

Methods

Patient Population, Treatment Strategies, and Study Endpoints

The design and results of TACTICS-TIMI 18 have been described previously.⁸ In brief, 2,200 patients with NSTEMI ACS were treated with unfractionated heparin, aspirin, and tirofiban, and were randomized to early invasive management within 4 to 48 h, versus a conservative management arm, reserving angiography and revascularization for spontaneously reoccurring instability or failed provocative studies for ischemia. At the time of randomization, patient data were recorded with the use of a standardized data form. Variables of interest included demographics, the results of history and physical examination, imaging results, management strategies, and outcomes.

Present Study

For the purpose of the present analysis, patients from TACTICS-TIMI 18 were categorized by the presence or absence of PAD as identified on the case report form. Peripheral arterial disease was defined as peripheral arterial atherosclerotic obstruction, and the diagnosis was based either on patient history or the impression of the managing physician. The interaction between PAD and baseline patient demographics and cardiac status was assessed, and the benefits of treatment with tirofiban followed by early invasive versus conservative management were examined as a function of the presence or absence of PAD.

The tolerability of catheterization among patients with PAD was examined, including rates of ischemic stroke following catheterization as well as bleeding events, the latter of which were assessed as described.⁸

Variables were compared using Fisher's exact test or the chi-square test for categorical data. Student's *t*-test was used for analysis of normally distributed continuous variables.

Results

Baseline Clinical Demographics

Of 2,219 patients in the study, 166 (7.5%) had PAD. The differences in baseline clinical characteristics based on the presence or absence of PAD are detailed in Table I, which identifies several significant differences between those pa-

tients with NSTEMI ACS and PAD and those without. Notably, patients with PAD had higher prevalence of several factors associated with risk in the setting of NSTEMI ACS, including more advanced age, a higher likelihood for prior CABG or diabetes mellitus, and a higher incidence of ST-segment depression on 12-lead electrocardiogram (ECG), when compared with patients without PAD in the TACTICS-TIMI 18 trial. Overall, this increased risk of patients with PAD is reflected in the TIMI NSTEMI ACS risk scores⁹ of this population, which were typically higher than those in patients without PAD; a TIMI risk score of ≥ 4 was more often seen among patients with PAD (56 vs. 41%, $p < 0.001$). When examined as a dual function of the presence or absence of PAD with respect to treatment assignment (early invasive versus conservative management), patient characteristics were well balanced (data not shown), although patients with PAD assigned to early invasive treatment were more likely to have NSTEMI acute myocardial infarction (MI) (47 vs. 26%, $p = 0.006$) and were more likely to have TIMI risk scores ≥ 4 (67 vs. 44%, $p < 0.001$) compared with patients with PAD randomized to the early conservative arm.

There was no significant difference in the extent or the severity of coronary artery disease, presence of coronary thrombus, or TIMI angiographic flow grade in patients with and without PAD (Table II).

Invasive versus Conservative Acute Coronary Syndromes Therapies

Of the 166 patients with PAD in the TACTICS-TIMI 18 trial, 79 (47.6%) were in the conservative arm, while 87 (52.4%) were in the early invasive arm.

Among patients in the conservative arm, 28 (35%) did not have angiography during their index hospitalization, while 51 (65%) failed conservative therapy and underwent angiography. Of the patients in the early invasive arm, all but five patients (94%) had angiography during initial hospitalization. Among all patients in this study, 47% underwent revascularization during their index hospitalization, which was similar to those patients without PAD (48%), and was essentially unchanged after 6 months of follow-up. In the subgroup of patients with PAD, compared with patients treated in the early invasive arm, those in the conservative arm were more likely to require CABG surgery during their initial hospitalization (37 vs. 20%, $p = 0.03$); however, rates of PCI (27 vs. 38%, $p = \text{NS}$) and medical therapy (36 vs. 42%, $p = \text{NS}$) were comparable between the two groups. Considering the composite of CABG and PCI overall, of those patients revascularized in the TACTICS-TIMI 18 trial, there was no difference between patients with and those without PAD with respect to rates of PCI either during index hospitalization (67 vs. 65%, $p = \text{NS}$) or at 6 months (65 vs. 63%, $p = \text{NS}$).

Outcomes

As expected, the frequency of ischemic NSTEMI ACS complications was higher among patients with than among those

TABLE I Baseline demographics among patients with or without peripheral arterial disease (PAD) in the TACTICS-TIMI-18 study

Variable	PAD (n = 166)	No PAD (n = 2,053)	p Value
Age, mean $\pm$ standard deviation	75 $\pm$ 10	62 $\pm$ 12	<0.001
Male gender (%)	70	66	0.261
Prior cardiac disease			
Angina pectoris (%)	12	13	0.725
Acute myocardial infarction (%)	54	38	<0.001
Coronary artery bypass graft (%)	39	20	<0.001
Percutaneous revascularization (%)	37	27	0.003
Congestive heart failure (%)	7	13	0.005
Risk factors			
Smoking (%)	31	27	0.259
Systemic hypertension (%)	81	65	<0.001
Diabetes mellitus (%)	38	27	0.002
Presenting syndrome of unstable angina (%)	36	37	0.768
Ischemia on electrocardiogram ^a (%)	63	59	0.345
Type of ischemia on electrocardiogram			
ST elevation (%)	13	11	0.446
ST depression (%)	43	29	<0.001
T-wave changes (%)	33	35	0.644
Concomitant therapy at presentation			
Nitroglycerin (%)	32	24	0.029
Aspirin (%)	99	98	0.280
Beta blocker (%)	81	81	0.980
TIMI risk score			
0–2 (%)	11	26	<0.001
3–4 (%)	63	60	0.439
≥ 5 (%)	26	14	<0.001

^a i.e., any ST changes (elevation, depression, or T wave).

TABLE II Results of angiography, expressed as a function of the presence or absence of peripheral arterial disease (PAD)

Variable	PAD (n = 166)	No PAD (n = 2,053)	p Value
Results of coronary angiography			
Extent of coronary artery disease			
1-vessel or none (%)	41	44	0.764
2–3 vessel (%)	59	56	0.764
Left main (%)	8	10	0.666
Thrombus present (%)	52	37	0.126
TIMI flow rate < 3 (%)	36	33	0.777

without PAD at both 30 days and 6 months (Fig. 1). Among patients with PAD, pretreatment with tirofiban followed by an early invasive strategy, compared with a conservative strategy, was associated with a significantly lower incidence of acute MI at 30 days (11.4 vs. 2.3%, $p = 0.03$). Furthermore, at 180 days, compared with early conservative management, early invasive treatment for patients with NSTEMI ACS and PAD was associated with similar reduction in acute MI (12.7 vs. 3.5%, $p = 0.04$), and was also accompanied by significant reduction in mortality (10.1 vs. 2.3%, $p = 0.05$).

Tolerability of Early Invasive Management for Patients with Non-ST-Segment Elevation Acute Coronary Syndromes and Peripheral Arterial Disease

The presence of PAD was not associated with an increase in the risk for hemorrhagic complications, and among patients treated with an early invasive strategy, there was no significant difference in bleeding rates compared with those patients without PAD or those with PAD treated conservatively (Table III); nor was the rate of ischemic stroke significantly higher among those patients with PAD treated invasively compared with invasively managed patients without PAD (0.2 vs. 0.6%, $p = \text{NS}$).

Discussion

We found that among patients with NSTEMI ACS and PAD there was a significantly higher prevalence of several factors associated with risk in the setting of NSTEMI ACS, including advanced age,¹⁰ prior CABG surgery,¹¹ diabetes mellitus,¹² severe ischemia on ECG,¹³ and higher TIMI NSTEMI ACS risk scores.⁹ It was not surprising, therefore, that patients with NSTEMI ACS and PAD had higher rates of ischemic complications in the TACTICS-TIMI 18 trial. We found that upstream treatment with tirofiban followed by early invasive manage-

FIG. 1 Effect of an early invasive strategy (I) versus a conservative (C) management strategy on the rates of ischemic complications of myocardial infarction (MI) or death among patients with non-ST-segment elevation (NSTEMI) acute coronary syndromes (ACS) both with and without peripheral arterial disease (PAD). At 30 days (A), significant reductions in risk of MI were present among invasively managed patients with PAD (11.4 vs. 2.3%, $p = 0.03$). By 180 days (B), similar reductions in risk of MI were present among invasively managed patients with PAD (12.7 vs. 3.5%, $p = 0.04$), accompanied by a significant reduction in the risk of mortality (10.1 vs. 2.3%, $p = 0.05$).

ment was well tolerated and associated with significant reductions in the high risk of morbidity and mortality among patients with NSTEMI ACS and PAD, lowering the risk for acute MI and/or death of the patient with PAD to the level of those patients without PAD.

Ischemic heart disease is highly prevalent among patients with PAD, who represent a particularly high-risk population in the setting of NSTEMI ACS.¹ In addition, the presence of PAD may be associated with increased risk of invasive procedures for ACS management, such as catheterization and PCI.³⁻⁶ Given both the high risk of ischemic complications and the potential risks associated with invasive management among patients with PAD, the identification of effective and well-tolerated strategies for management of NSTEMI ACS in such patients is important.

Among certain high-risk ACS subgroups, platelet GP IIb/IIIa receptor antagonists are beneficial, particularly when used in an early invasive strategy with routine cardiac catheterization and revascularization.^{8, 14} Although prior studies have examined the use of GP IIb/IIIa receptor antagonists such as tirofiban for peripheral angiography and intervention among patients with PAD,⁷ the efficacy and tolerability of the combination of tirofiban with an early invasive management for patients with PAD and NSTEMI ACS remained unclear. Our results are therefore useful to guide optimal management for this high-risk ACS subgroup.

The mechanisms of benefit for those patients with NSTEMI ACS and PAD in our study may, in part, be related to ad-

vances in both the medical and interventional therapies utilized, including platelet GP IIb/IIIa receptor antagonism in every patient, as well as the frequent use of coronary stents among patients treated invasively. Despite treatment with aspirin, patients with PAD may still have a higher than expected risk for ischemic vascular complications, including coronary events, and it has been suggested that such patients may be more likely to benefit from the use of more highly potent antiplatelet therapy.¹⁵ This salutary response to vigorous antiplatelet therapy has been suggested to be reflective of either more widespread platelet activation among patients with PAD, suboptimal response of these patients to the modest effects of aspirin, or both.¹⁶⁻¹⁸

Our study has a major limitation in that the diagnosis of PAD was made based on patient histories and/or on the impression of the managing physician, rather than by using a standardized method for the detection of PAD, such as the ankle-brachial index, a relatively sensitive method for noninvasive detection of PAD, whose results are also correlative with cardiovascular risk.¹⁹ As true prevalence of PAD is typically underestimated in at-risk patient populations,²⁰⁻²² the likelihood is that more patients in our study had PAD but were not classified as such. It is remarkable that irrespective of the lack of corroborative data supporting the diagnosis, the identification of a PAD history in a patient with an NSTEMI ACS in the TACTICS-TIMI 18 trial was able to identify a mortality benefit from early invasive management. Another limitation includes the lack of prospectively gathered data regarding vas-

TABLE III Bleeding rates stratified by the presence of peripheral arterial disease (PAD) and treatment assignment with early invasive (I) versus conservative (C) non-ST-elevation acute coronary syndrome therapy

Variable	PAD		p Value for I vs. C	No PAD		p Value for I vs. C
	I	C		I	C	
TIMI major bleeding	0	0	N/A	2.14	1.17	0.084
TIMI minor bleeding	4.60	2.53	0.684	3.12	2.14	0.168
All TIMI bleeding	4.60	2.53	0.684	5.06	3.12	0.026

cular access site for angiography. Furthermore, although we present data regarding hemorrhagic complications subsequent to angiography and early stroke related to catheterization, we do not have available data regarding ischemic complications among patients with PAD and NSTEMI ACS who underwent angiography.

Conclusion

Our data suggest that for patients with NSTEMI ACS and PAD in the TACTICS TIMI-18 study, upstream treatment with tirofiban followed by a routine invasive management strategy was associated with an acceptable risk and was accompanied by considerable benefit, including a significant reduction in the risk for MI and mortality, compared with patients with NSTEMI ACS and PAD treated with a more conservative, ischemia-driven management strategy.

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